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Winner of the IUPAC Prize for Young Chemists - 2003

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Gonzalo Cosa wins one of the 5 IUPAC Prize for Young Chemists, for his Ph.D. thesis work entitled "Mechanism of Degradation of Pharmaceutical Products and Analogues, and Development of a Novel Fluorescence Technique for DNA-damage Detection."

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Academic degrees

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Ph.D. Thesis

Title Mechanism of Degradation of Pharmaceutical Products and Analogues, and Development of a Novel Fluorescence Technique for DNA-damage Detection
Adviser Prof. J.C. (Tito) Scaiano
Thesis Committee Prof. Jean Cadet, Dep. de Recherche Fondamentale sur la Matiere Condensee, Grenoble, France; Prof. Alex Fallis, Dep. of Chemistry, University of Ottawa; Prof. P. Mayer, at University of Ottawa; Prof. J.S. Wright, Dep. of Chemistry, Carleton University, Ottawa, Canada

Essay

Photochemistry in biological systems has received an ever-increasing attention in the last few years. This is due to the

many practical applications of the field, examples of which are phototherapy in cancer treatment, as well as the development of new diagnostic procedures. Interest is also triggered by the deleterious effects that sunlight is producing in human body as result of an increase in the UV portion of the sun spectrum reaching the earth surface. Damage can be best summarized by skin photosensitization reactions and radiation induced mutations.

At the time of initiating my graduate studies I was interested in areas of biological significance where research would have a direct impact on our quality of life. I thus pursued a molecular level understanding of the effect of UV radiation in our organism. I also worked on the application of photochemical techniques for diagnostic procedures. My graduate research project in photochemistry in biological systems thus encompassed three very important and interconnected aspects related to solar radiation and human health: prediction, prevention, and diagnosis.

Toxic reactants are a common result of the interaction of sunlight with pharmaceutical agents transported in the blood system or applied topically. It was striking to observe that both the anti-inflammatory agent ketoprofen as well as the hypolipidaemic drug fenofibric acid were closely related to benzophenone (Figure 1). The latter is the longest known and best understood model of radical like activity following light absorption.

In the case of ketoprofen, time resolved experiments established an efficient singlet state mediated decarboxylation, occurring within picoseconds, and followed up by protonation of the resulting carbanion in a few nanoseconds. This fast deactivation ruled out the involvement of the excited state or any of the subsequent intermediates in adverse photosensitization effects. A similar situation aroused for fenofibric acid, which rapidly, (i.e., within hundreds of nanoseconds) decayed to starting material or photoproducts. Given these fast decays characterizing the longer lived transients of ketoprofen and fenofibric acid, oxygen involvement in their deactivation in the living tissues was predicted not to play a major role. The phototoxicity reported for these molecules was therefore explained by their efficient generation of photoproducts. These photoproducts lack a fast deactivation mechanism following photoexcitation and are prone to undergo Type I reactions with cellular components, or Type II reactions with oxygen in the cell, as has been established to be the case with benzophenone.

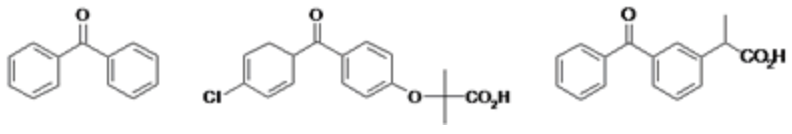
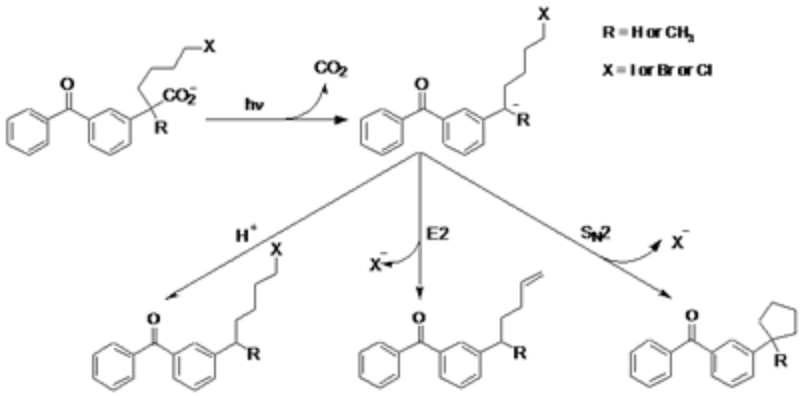


Figure 1. From left to right: structure of benzophenone and the drugs fenofibric acid and ketoprofen.

The possibility of generating a carbanion within the duration of a laser pulse was very attractive for mechanistic studies. Thus ketoprofen photogenerated carbanion grasped our attention as an exciting substrate to study in order to better understand the chemistry of carbanions in different systems like water or DMSO. With this in mind, we examined different ketoprofen derivatives. Upon photoexcitation, and subsequent decarboxylation, these derivatives were expected to render their respective carbanions which would in turn react with water or undergo an intramolecular S_N2 or E2 reaction (see Scheme 1). Every textbook in Organic Chemistry dedicates one or more chapters to nucleophilic substitution, one of the most versatile reactions in chemical synthesis, yet not a single absolute rate constant is known for carbanions. Our work established those values for the first time, as well as protonation rate constants for these carbanions.



Scheme 1. Reactions of 1-(3-benzoyl-phenyl)-alkyl carbanions.

We also investigated the capability that naturally occurring as well as artificially generated protective substrates have to prevent damage from both solar radiation and its undesired photoproducts. This lead to preliminary work on new sunscreens based on the novel concept of isolation of the photoactive ingredient within a chemically inert, transparent framework, as given by zeolite cages. We also determined the feasibility of formation of the natural occurring protective pigment melanin as a result of degradation of its precursors in the presence of light-elicited toxins. Thus the properties of the adrenaline derived radical were evaluated, as a case study for the catecholamine group in general. Absolute rate constants for tert-butoxyl radical scavenging and triplet benzophenone quenching were reported, and a reactivity comparison was established with other intermediates involved in the reaction of melanin formation via catecholamines.

Equally interested in the diagnosis of radiation damage, we developed a novel technique for the rapid evaluation of DNA

damage. This technique is based on the photophysical behavior of DNA fluorescent probes. It allows one to determine damage exerted by the phototoxic agents to the nucleic acid, the genetic information carrier and a common target of the previously mentioned agents. The rigidity imposed by the DNA base pairs on intercalating chromophores was exploited (Figure 2). Its retardation effect on the relaxation of a photoexcited DNA-stain probe was employed to determine the amounts of DNA existing as double and single stranded form; which is ultimately an expression of the damage the DNA has suffered.

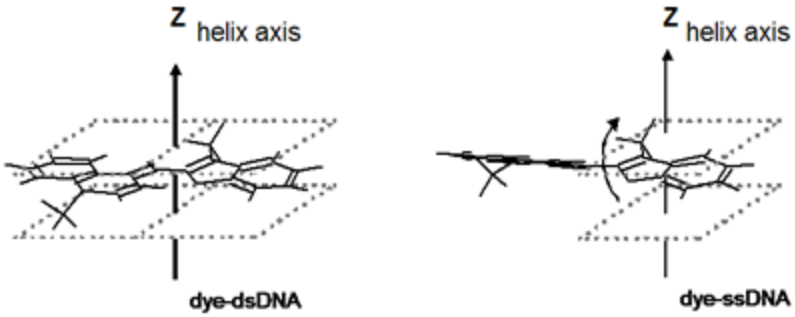


Figure 2. Schematic representation of dye-dsDNA and dye-ssDNA complexes; z is the direction of the helix axis. The planes represent the DNA bases. Following excitation twisting along the methine bridge converts the molecule into the excited perpendicular singlet state wherefrom it decays nonradiatively. This internal rotation is far more restricted in double stranded DNA, as compared to single stranded DNA.

In summary, our work allowed us to establish a systematic approach for studying the mechanism of degradation of pharmaceutical products using fast spectroscopy techniques. These studies are essential to predict (and eventually prevent) the appearance of phototoxic and photoallergic side effects. An understanding of dye-DNA interactions was also gained, and employed in the diagnosis of radiation elicited DNA damage. Preliminary studies also showed the feasibility of elaborating sunscreens based on the novel concept of encapsulation, which is aimed at preventing the side effects present in many current sunscreen photoactive ingredients.

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